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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/235,986	01/22/99	HENDRICKSON	W 58323/JPW/PT

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HM12/0618

EXAMINER

LUNDGREN, J

ART UNIT

PAPER NUMBER

1631

DATE MAILED:

06/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/235,986.

Applicant(s)

HENDRICKSON ET AL.

Examiner

Jeffrey Lundgren

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 1 and 7 for reciting the phrase "corresponding homologous sequence information", as it is not clear which sequences which sequence would be determined to have "corresponding homology" and the sequences that do not, as would be reasonable for establishing the families. Applicants can overcome this rejection by deleting the term "corresponding".

All other rejections under 35 U.S.C. 112, second paragraph, in the Office Action mailed on December 14, 2000, are overcome by either amendment or argument in the response received on April 20, 2000.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The rejection of claims 1, 3, 5-7, 9, and 11-12, under 35 U.S.C. 103(a) as being unpatentable over Bachar et al. (Protein Engineering 6, 279-288, 1993), in view of Hendrickson et al. (The EMBO Journal 9, 1665-1672, 1990), in view of Everett et al. (Nature Genetics 17, 411-422, 1997), in view of Andrea et al. (J. Med. Chem. 34, 2824-2836, 1991), in the Office Action mailed on December 14, 2000, is maintained.

In the response received on April 20, 2001, Applicants argue that Bachar does not teach the use of sequence alignment as an approach to the comparison of protein structures. Applicants argue that Hendrickson paper fails to teach organization of sequence information, clustering, and synthesizing. Applicants argue that Everett does not describe a database of sequence information, a bioinformatics tool, protein synthesis means, homology model building means, and a database updating means. Applicants argue that Andrea does not teach three-dimensional protein structures.

Applicants arguments have been fully considered, however, are not found persuasive for the reasons below.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Bachar teaches a method/system for protein classification, wherein an experimentally-derived, three-dimensional structure of a target protein can be classified by assignment to a cluster set of structurally similar, three-dimensional representation of proteins in an organized database. The design and organization of the database consists of three major steps: 1) finding relatively small subset of the structures that

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form an initial match; 2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues. These steps are further comprised of sub-steps detailed in the disclosure (pages 280-283). Bachar teaches *both* the well-known *sequence dependent approach* in the art to an initial classification step, as well as a *sequence independent approach* for initial classification steps of target proteins to those of a database (see page 286). These well-known homology comparison approaches are demonstrated by Everett, wherein the classification of an unknown protein is first carried out through a sequence dependent approach. Everett discloses a method/system for characterizing/clustering proteins into families based on their sequence and structure, such as using their linear sequence and by characterizing transmembrane regions using PHDhtm (see *Computational analysis of PDS and its encoded protein*). Everett then assigns a function to an unknown protein based on the similarity comparison of the target protein to the proteins which have been clustered into families which also have functional information. For example, a function of sulfate transport is assigned to pendrin based on the family clustering model which classified pendrin in the family of other sulfate transporters, and the observed physiological effects that are present which correlate with sulfate transport deficiency in those diagnosed with Pendred syndrome (see PDS mutations in Pendred-syndrome families). Everett discloses that these bioinformatics tools are advantageous in that they reduce experimental efforts of trial and error, wherein researchers would otherwise be uncertain of the target protein's function (see *Discussion*). Combined with the invention of Bachar, these limitations of Applicants' claimed invention are disclosed and obvious, as both Bachar and Everett recognize the usefulness of sequence dependent alignment.

Furthermore, although the focus of Bachar is in proteomics wherein protein classification is based on the x-ray crystallographic data, and *not* in the instrumental improvements of x-ray crystallography, one of ordinary skill in the art would recognize that improvement analytical methods for obtaining data with higher precision and/or resolution would be beneficial to the bioinformatics tool of Bachar. Hendrickson teaches a system and process for incorporating selenomethionine (as a replacement for

methionine) into recombinant proteins produced from plasmids in *E. coli.*, which are crystallized and analyzed by multiwavelength anomalous diffraction (MAD) as a means for producing a three-dimensional representation of a target protein. Their method provides the advantages over conventional x-ray techniques for elucidating three-dimensional protein structures, in that MAD utilizes the scattering effects of resonance between x-rays and bound atomic orbitals, it is perfectly isomorphic, allows for data sampling from a single crystal, and the analysis is algebraically exact (see *Introduction*).

Additionally, one of ordinary skill in the art would have recognized the advantages the classification system as taught by Andrea with the proteomics tool of Bachar. Neural networks, as disclosed by Andrea, are dynamic classification systems useful in modeling the non-linear function of several variables, wherein classification of a changing population of subjects within a database can be carried out. One would recognize that the refined model and structure of the experimentally examined protein would provide an improved and refined overall model, and the physicochemical features of the refined target protein whose structure has been determined could be applied to the other protein family members which were originally classified based on sequence information. One of ordinary skill in the art would also be motivated to implement the QSARs methodology as disclosed by Andrea, as a means to determine which chemical structures (or family/class of chemical structures) associate with a given protein structure (or family thereof).

The rejection is maintained.

6. The rejection of claims 4 and 10, under 35 U.S.C. 103(a) as being unpatentable over Bachar, Hendrickson, Everett, and Andrea, as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Lima et al. (Structure 5, 763-774, **1997**), in the Office Action mailed on December 14, 2000, is maintained.

In the response received on April 20, 2001, Applicants argue that Lima does not teach such elements as a database of three-dimensional structures representing proteins, sequence based alignment, and a bioinformatics tool for data manipulation.

Applicants arguments have been fully considered, however, are not found persuasive for the reasons below.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, although the focus of Bachar is in proteomics wherein protein classification is based on the x-ray crystallographic data, and *not* in the instrumental improvements of x-ray crystallography, one of ordinary skill in the art would recognize that improvement analytical methods as taught by Lima for obtaining data with higher precision and/or resolution would be beneficial to the bioinformatics tool of Bachar. Lima et al., teach using an undulator beamline x-ray source, with MAD because of the high output levels, with narrow, tunable, harmonic peaks (see *Results and Discussion*).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the undulator beamline x-ray source, in place of the synchrotron device as taught by Hendrickson et al., because Lima et demonstrate of a high output x-ray source, with narrow, tunable, harmonic peaks. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

The rejection is maintained.

7. The rejection of claims 2 and 8, under 35 U.S.C. 103(a) as being unpatentable over Bachar, Hendrickson, Everett, and Andrea, as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Craig et al., (U.S. Patent No. 5,525,198, June 11, 1996), in the Office Action mailed on December 14, 2000, is maintained.

In the response received on April 20, 2001, Applicants argue that Craig does not teach such elements as a database of three-dimensional structures representing proteins, sequence based alignment, and a bioinformatics tool for data manipulation.

Applicants arguments have been fully considered, however, are not found persuasive for the reasons below.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Although the focus of Bachar is in proteomics wherein protein classification is based on the x-ray crystallographic data, and *not* in the instrumental improvements of x-ray crystallography, one of ordinary skill in the art would recognize that improvement analytical methods as taught by Craig for obtaining data with higher precision and/or resolution would be beneficial to the bioinformatics tool of Bachar. Craig et al., teach the cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to x-ray sources (column 5, lines 3-18).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a means for the cryogenic cooling of the target protein crystal, with the system/process of Bachar et al., in view of Hendrickson et al., as Craig et al., teach that cryogenic cooling preserves crystals during x-ray sampling. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

The rejection is maintained.

Conclusion

8. No claims are allowable.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiries concerning the *merits* of this communication or earlier communications from the Examiner should be directed to Jeffrey S. Lundgren, whose telephone number is (703) 306-3221. The Examiner can normally be reached on Monday-Friday from 7:00 AM to 5:00 PM (EST).

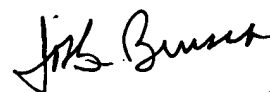
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Michael Woodward, can be reached at (703) 308-4426.

Any inquiries of a *general* nature relating to this application should be directed to Ms. Pauline Farrier, Patent Analyst for Art Unit 1631, whose telephone number is (703) 305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1631 using (703) 308-0294. Please notify the Examiner of incoming facsimiles prior to sending papers to the aforementioned fax number. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).



Jeffrey S. Lundgren, Ph.D.



JOHN S. BRUSCA, PH.D.
PRIMARY EXAMINER